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Informed Consent for Alzheimer's Disease Clinical Trials: A Survey of Clinical Investigators

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Informed Consent for Alzheimer's Disease Clinical Trials:

A Survey of Clinical Investigators

BY JASON H.T. KARLAWISH, DAVID KNOPMAN, CHRISTOPHER M. CLARK, JOHN C. MORRIS, DANIEL MARSON, PETER J. WHITEHOUSE, AND CLAUDIA H. KAWAS

Informed consent is fundamental to the responsible conduct of human subjects research (45 CFR 46.111(4)). A subject's voluntary, competent, and informed decision to enroll in research fulfills the ethical principle of respect for autonomy. Unfortunately, this goal is difficult to achieve in research that involves subjects whose ability to make decisions is impaired.

Patients with Alzheimer's disease represent one of the commonest examples of these kinds of subjects. Compared to nondemented individuals matched for age and education, many AD patients have impairments in their capacities to understand, appreciate, and reason about information.^{1,2} These impairments may be sufficiently severe to preclude the ability to provide informed consent.

While this raises considerable concern among investigators, patient advocates, and health policymakers, there has been very little study of the actual practice of informed consent in AD clinical trials.³ A survey of policies at 29 Alzheimer's Disease Centers funded by the National Institute on Aging

(NIA) found that half do not have written policies or formal guidelines beyond the existing federal and state regulations,⁴ and each site's unique institutional review board requirements,⁵ which do not describe how informed consent is actually obtained for clinical trials that involve patients with dementia.

It is important, however, to know what the process of informed consent is at individual sites participating in a specific clinical trial in order to identify any variations that exist among sites. These variations may include differences in recruitment methods, methods used to identify potential subjects or determine competency, and rules regarding who can serve as a proxy for a noncompetent patient. Until such data are known, we run the risk that AD clinical research may be conducted in a manner that does not acceptably balance competing interests in promoting research and protecting subjects. Thus to better understand the process of informed consent for AD clinical trials, we surveyed the member institutions of a cooperative network of AD clinical research sites. The institutional review board at the University of Pennsylvania approved the survey.

Jason H.T. Karlawish, David Knopman, Christopher M. Clark, John C. Morris, Daniel Marson, Peter J. Whitehouse, and Claudia H. Kawas, "Informed Consent for Alzheimer's Disease Clinical Trials: A Survey of Clinical Investigators," *IRB: Ethics & Human Research* 24 No. 5 (2002): 1-5.

Informed Consent Processes among ADCS Sites

Thirty-nine sites participating in the Alzheimer's Disease Cooperative Study (ADCS), a NIA-funded network of AD clinical programs and investigators, were eligible for this survey. The survey used both fixed-choice and open-ended questions to determine how the sites conducted the informed consent process and what state laws, regulations, and local rules governed informed consent. Respondents answered on the basis of their most recent clinical trial that involved community-dwelling patients with mild to moderate Alzheimer's disease.

Because the consent process begins with the first contact with a potential subject, our questions covered subject recruitment as well as the informed consent session. After revisions based on a pilot test to five sites, we distributed the survey via electronic mail to the principal investigators (PIs) at each of the 39 sites with a request that it be completed by the person most familiar with the informed consent process for clinical trials.

Thirty sites returned the survey for a response rate of 77%. Two individuals independently coded the answers to all open-ended questions. We present the data with appropriate summary statistics. For some questions, missing data reduces the total number of respondents.

Respondents were generally either a principal investigator (n=17, 57%) or study coordinator (n=10, 33%). The majority of the surveys focused on the informed consent process for an ADCS clinical trial to assess the safety and efficacy of non-steroidal anti-inflammatory agents for patients with mild to moderate AD (n=23, 77%) (Mini-Mental State score 13 to 26 inclusive).

Subject Recruitment

Respondents identified all persons at their site who recruited sub-

Table 1.
Persons performing recruitment and the proportion of effort contributed to recruitment.

Recruiter	# of sites ¹	Percent of recruitment done by recruiter Mean ± S.D. (range)
Study coordinator	29	53% ± 28 (10 - 100%)
Site Principal Investigator	23	39% ± 26 (10 - 100%)
MD clinician	5	14% ± 13 (0.5 - 35%)
RN clinician	6	21% ± 17 (5 - 50%)
Co-Principal investigator	6	41% ± 22 (10 - 70%)
Other ²	13	20% ± 21 (4 - 75%)

¹Total number of sites is > 30 because some sites have more than one person as a recruiter.

²Other includes clinic manager, data coordinator minority outreach, director of medical education, information and referral coordinator, medical coordinator, outreach worker, program administrator, psychometrician, research assistant, social worker.

jects for the trial, assigned each person's percent effort for the recruitment, and indicated whether potential subjects and their caregivers received any informational materials during recruitment. The number of persons per site who recruited subjects ranged from one to four: one person recruited at four sites (13%), two persons at nine sites (30%), three persons at 11 sites (37%), and four persons at six sites (20%). Table 1 lists the professional roles of persons who recruited subjects, and

each person's proportion of recruitment. The study coordinator (29 sites) and PI (23 sites) performed the largest proportion of recruitment, followed by "other people," who included a variety of clinical care, social work, and administrative staff.

All but one site provided some kind of informational materials during recruitment: 67% (20/30) of the sites routinely provided the informed consent form prior to the informed consent visit; 57% (17/30)

Table 2.
Persons who perform informed consent

Number of sites	Number of people conducting I.C.	Identity of people conducting I.C.
20	1	Study Coordinator= 14 PI=4 Nurse clinician=1 Co-PI=1
8	2	Study Coordinator=6 PI=7 Other=8
2	3	Study Coordinator=2 PI=2 Physician clinician=1 Co-PI=1

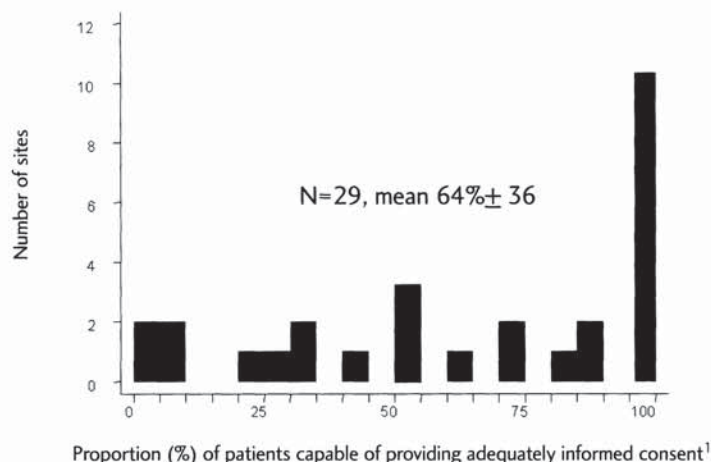
provided materials describing the study; and 30% (9/30) provided materials to assist potential subjects in thinking about whether to enroll in research. Among the 10 sites that did not routinely provide the informed consent form during recruitment, several noted concern that the form might confuse potential subjects, especially those with low education.

The Informed Consent Session

Each site reported the following: who conducts informed consent, whether any materials are used in addition to the consent form, the methods used to assess patient and caregiver decisionmaking capacity, and the state laws or regulations and local rules that governed the informed consent process. The number of persons per site who performed informed consent was one person at 20 sites (67%), 2 persons at 8 sites (27%), and 3 people at 2 sites (10%). Table 2 shows that either the study coordinator (22 sites) or the PI (14 sites) most often solicited informed consent. At all but seven sites, the coordinator was responsible alone or in concert with other staff for obtaining informed consent. During the consent conversation, 10 sites (33%) use materials in addition to the consent form to inform the patient and caregiver about the trial. Sites reported that these materials were typically short summaries of the informed consent form.

Four sites (17%) reported that they use materials to assess caregiver decisionmaking capacity, and 12 sites (40%) reported that they use materials to assess patient decisionmaking capacity. These included cognitive testing (5 sites), a clinical interview (3 sites), assessments of the domains of decisionmaking capacity modeled after the domains and methods developed by Marson and colleagues⁶ (3 sites), and a capacity-to-consent questionnaire (1 site). No site reported using the MacArthur Competency Assessment

Figure 1.
Proportion of mild to moderate stage Alzheimer's disease patients capable of informed consent for a clinical trial



¹Twenty-three sites reported on the same clinical trial that enrolled patients with mild to moderate AD.

Tool for Clinical Research.⁷

Figure 1 shows the range of answers to the question,

What proportion of AD patients who were enrolled were capable of providing an adequate informed consent? "Adequate informed consent" means that the patient understands the research purpose, risks and benefits, and alternatives; appreciates the consequences of participating; considers the alternatives; and makes a voluntary choice.

The proportions range from 0 to 100% of patients (mean 64% ± 36%). One site reported that patient and caregiver together constitute 100% capacity to consent. The 23 sites reporting the consent process for the nonsteroidal anti-inflammatory agent clinical trial had the same distribution.

Proxy Consent Practice

To identify respondents' knowledge of the state laws or regulations, or local rules that governed informed consent each respondent answered two questions. First, "Are there laws or regulations that describe the kinds of persons who have the authority to provide informed consent to research that involves an adult who is not compe-

tent to provide an informed consent?" Thirteen (45%) respondents reported there were laws or regulations, 10 (34%) reported there were no laws or regulations, and 6 (21%) did not know. Five respondents incorrectly stated that there are laws governing research consent for incapacitated adults when in fact no laws or regulations exist in their jurisdictions. Seven respondents located in states with laws or regulations⁸ reported either that no laws or regulations exist or that they did not know whether they exist.

The second question asked whether any laws or local IRB rules describe who can provide proxy informed consent for an adult who is not competent. Figure 2 shows the distribution of respondents' answers to whether proxy consent alone is sufficient to permit enrolling an incapacitated adult in a clinical trial, and the breakdown of persons who can serve as proxy. At 17 sites (57%), a family member was among the potential proxies. At 8 (28%) sites, the proxy was a legally authorized decisionmaker (guardian or power of attorney). Four sites (14%) reported that no one can provide proxy consent.

Improving the Consent Process for Decisionally Impaired Subjects

Informed consent is a key ethical and legal component in assuring that research subjects are adequately protected. In the case of research that involves persons with AD, this goal is difficult to fulfill. Our survey reveals substantial variation in the practices of informed consent even within a national network of Alzheimer's disease clinical research centers engaged in studies that involve patients with mild to moderate AD. These results suggest potential opportunities to develop and disseminate best practices.

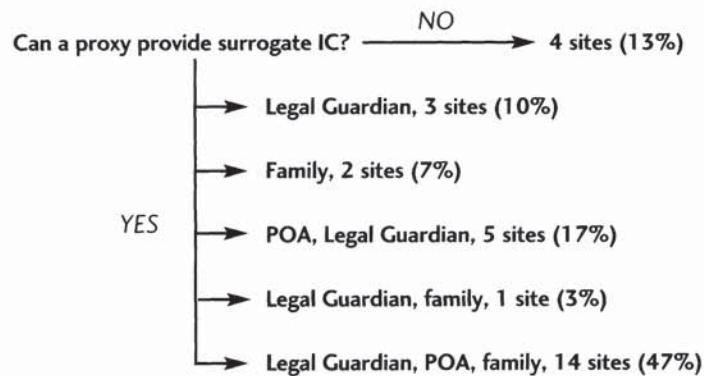
It was common among sites to have multiple persons recruit subjects, and to hand out the consent form during recruitment as a way of beginning to inform prospective subjects about a given study. Sites differed, however, in whether they provided other materials that describe the study, and/or materials to assist in thinking about enrolling in research.

During informed consent sessions, most sites rely on one person—usually the study coordinator—to obtain consent. But again, there are differences across sites. One-third of the sites use materials in addition to the consent form to assist in describing the trial.

Practices to assess patient and caregiver decisionmaking capacity also vary. Specifically, just under half of the sites use materials to assess patient decisionmaking capacity. The materials that are used vary from psychometric testing to clinical interviews to assess the domains of decisionmaking capacity.

These differences likely explain some of the variability in the proportions of mild to moderate stage AD patients identified by the persons conducting informed consent as being capable of giving adequately informed consent. Other factors that would explain this variability, which

Figure 2.
Respondents reports of who their IRB allows to serve as a proxy decision-maker for informed consent in AD clinical trials



we did not study, include the study coordinator's background and training and variations in the severity of patient cognitive impairment.

Sites show considerable variation with regard to whether a family member can serve as a proxy and whether the proxy must be legally authorized as the patient's decision-maker, as well as in their understanding of relevant state laws and regulations. Notably, the four sites (14%) which asserted that no one can provide proxy informed consent also reported proportions of AD patients who were capable of an adequate informed consent of 100%, 95%, 85%, and 20%.

Finally, seven sites either did not know or thought no laws or regulations exist that describe the kinds of persons who have the authority to provide proxy informed consent when in fact they were from states that have laws or regulations regarding proxy decisionmakers. Some of these respondents may have interpreted this question with respect to whether laws or regulations specifically govern research that involves community-dwelling AD patients. This interpretation is defensible in light of the fact that, with the exception of California, the majority of state laws can be interpreted to apply solely to research

that involves residents of state mental health facilities.⁹ Most such laws do not mention dementia or AD.

Taken together, these data suggest a number of areas for further study and potential improvements to the informed consent process in AD clinical trials. The study coordinator is clearly a key person in the consent process, as surveys of psychiatric researchers also show.¹⁰ Further research should determine what training study coordinators' receive about informed consent; and interventions to improve informed consent should certainly include input from and address education of coordinators. Further, investigators may want to test whether materials that summarize a study and assist potential subjects in thinking about the decision whether to enroll affect both enrollment rates and patient and caregiver comprehension and satisfaction with recruitment and informed consent.

There is also potential to improve practices for assessing decisionmaking capacity and competency. The wide range in the proportions of patients with mild to moderate AD the survey sites identified as capable of giving adequately informed consent suggests significant variability in how investigators assess decisionmaking capacity and competency.

Although no single measure of patient cognition determines that an AD patient has adequate decision-making capacity,¹¹ some sites rely on cognitive testing to assess that capacity. And there is variability among other methods used by sites that do not rely on cognitive measures to assess decisionmaking capacity. These findings suggest a need to identify and test the feasibility, reliability, and validity of these and other instruments in order to identify and disseminate best practices to all sites, especially when valid instruments already exist to assess the capacity of AD patients to make decisions about participating in research.¹² In addition, a structured assessment approach can improve the reliability of physician assessments of AD patient competency.¹³

Finally, the differences across sites' understanding of whether proxy consent is permissible and, if it is, who can serve as a proxy, show that sites need education on local laws and regulations.

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The authors are members of the Internal Ethics Committee of the Alzheimer's Disease Cooperative Study.

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